AAC Journals.ASM.org

Effect of Posaconazole on Cyclosporine Blood Levels and Dose Adjustment in Allogeneic Blood and Marrow Transplant Recipients

Isabel Sánchez-Ortega,[a,b] Lourdes Vázquez,[c] Carmen Montes,[d] Beatriz Patiño,[a,e] Montserrat Arnan,[a,e] Arancha Bermúdez,[d] Lucrecia Yáñez,[d] Teresa Caballero,[c] and Rafael F. Duarte[a,e]

Department of Clinical Hematology, Catalan Institute of Oncology, Hospital Duran i Reynals, Barcelona, Spain[a]; Universitat Autònoma de Barcelona, Campus UAB, Bellaterra, Barcelona, Spain[b]; Department of Hematology, Hospital Universitario de Salamanca, Salamanca, Spain[c]; Department of Hematology, Hospital Universitario Marqués de Valdecilla, Santander, Spain[d]; and Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet de Llobregat, Barcelona, Spain[e]

The posaconazole prescribing information recommends an upfront cyclosporine dose reduction upon initiation of posaconazole prophylaxis. We examined this recommendation in the early phase of allogeneic transplantation, where cyclosporine levels potentially becoming subtherapeutic following upfront dose reduction would be deleterious to transplant outcome. Our data show that while posaconazole leads to an increase in cyclosporine levels, subsequent cyclosporine dose reduction can be safely guided by therapeutic drug monitoring and is not required upfront. Therefore, the current recommendation may be modified.

Posaconazole is a novel triazole with broad-spectrum antifungal activity and a favorable toxicity profile (4, 7) that is currently approved for primary antifungal prophylaxis in allogeneic blood and marrow transplantation (allo-BMT) recipients with graft-versus-host disease (GVHD) (18). Posaconazole prophylaxis in allo-BMT recipients is normally administered in combination with immunosuppressive drugs for GVHD prophylaxis and/or treatment, most commonly cyclosporine (CsA). On the basis of its CYP3A4-inhibitory activity, posaconazole increases the exposure to CsA, warranting a recommendation for close monitoring of blood CsA levels and subsequent CsA dose adjustment, as required. It is noteworthy that the posaconazole prescribing information also includes a recommendation for upfront reduction of the dose of CsA upon initiation of combined treatment (17), which emerged from a very small study of cardiac transplantation (16) and has never been analyzed in allo-BMT recipients. In these patients, the potential occurrence of subtherapeutic blood CsA levels, even transiently, has a strong negative impact on GVHD and on the outcome of allo-BMT (5, 6, 11, 12, 14, 19). The clinical need for such an upfront CsA dose reduction in patients starting posaconazole in this clinical setting ought to be studied.

We have recently reported on the clinical efficacy and safety of primary antifungal prophylaxis with posaconazole during the early phase of allo-BMT (15). Here we present an analysis of the impact of posaconazole prophylaxis on CsA management in this clinical setting. Since potential subtherapeutic blood CsA levels pose the highest risk during the early posttransplant period, for this study we prospectively decided not to reduce the dose of CsA at the start of combined treatment with posaconazole. Instead, blood CsA levels were monitored at least three times weekly and the dose was adjusted as required to maintain trough CsA levels within the therapeutic range (125 to 300 ng/ml) or if CsA-related toxicity occurred. Other than this, all patients received posaconazole in keeping with the recommendations for administration in the product prescribing information. A total of 41 recipients of a first allo-BMT were included in this study (Table 1), with institutional approval by the clinical research ethics committee (CEIC Bellvitge; EPA 008/08). Patients were on steady-state CsA twice daily as a 2-h intravenous infusion for GVHD prophylaxis and started receiving 200 mg of an oral posaconazole suspension three times daily the day following transplantation. The primary endpoints included the trough CsA concentration, CsA dose adjustment, the CsA concentration-to-dose ratio, and clinical toxicity. Endpoints were assessed on days 0 (at initiation of combined

TABLE 1 Patient demographics and transplant characteristics

Parameter	Value
No. of patients	41
Median age in yr (range)	51 (18–68)
No. (%) of:	
Males	25 (61)
Females	16 (39)
Median wt in kg (range)	71.3 (48–104)
No. (%) with underlying disease	
AML/MDS[a]	29 (71)
CLPD[b]	9 (22)
Other	3 (7)
No. (%) with donor type	
Related	25 (61)
Unrelated	16 (39)
Matched	33 (80)
Mismatched	8 (20)
No. (%) with conditioning regimen	
Myeloablative	12 (29)
Reduced intensity	29 (71)

[a] AML/MDS, acute myeloid leukemia/myelodysplastic syndrome.
[b] CLPD, chronic lymphoproliferative disease.

Received 19 July 2012 Returned for modification 25 August 2012
Accepted 22 September 2012
Published ahead of print 1 October 2012
Address correspondence to Rafael F. Duarte, rduarte@iconcologia.net.

doi:10.1128/AAC.01489-12

TABLE 2 Impact of antifungal prophylaxis with posaconazole on the blood CsA level, dose adjustment, and concentration-to-dose ratio in allogeneic BMT recipients[a]

Time point	Blood CsA level (ng/ml)	*P* value	CsA dose (mg/kg/day)	*P* value	CsA level/dose ratio	*P* value
Day 0	225.8 ± 119.3 200 (85–598)	0.028[b]	3.09 ± 1.01 3.01 (1.32–5.17)	0.857[b]	82.1 ± 72.2 64.5 (26.6–449.6)	0.108[b]
Day 7	293.1 ± 150.9 256.0 (92–873)	0.478[c]	3.06 ± 1.10 3.01 (0.63–5.63)	0.082[c]	113.1 ± 90.5 83.5 (21.1–525.4)	0.158[c]
Day 14	304.9 ± 132.9 284.5 (72–719)	0.009[d]	2.61 ± 1.15 2.63 (0.63–5.63)	<0.001[d]	138.0 ± 80.3 114.7 (26.1–424.5)	0.072[d]
Day 30	245.8 ± 121.8 221.0 (89–702)	0.011[e]	1.58 ± 0.82 1.34 (0.53–4.50)	0.028[e]	172.6 ± 76.2 171.3 (64.5–375.4)	<0.001[e]

[a] Data are expressed in all cases as the mean ± standard deviation, median, and range. *P* values for changes across the study period were measured by one-way ANOVA, and those for comparisons between specific time points were measured with the Student *t* test for paired data.
[b] *P* value for the comparisons between days 0 and 7.
[c] *P* value for the comparisons between days 7 and 14.
[d] *P* value for the comparisons between days 14 and 30.
[e] *P* value for changes across the study period.

treatment), 7, 14, and 30 and at least three times weekly, except for clinical toxicity, which was evaluated daily. Whole-blood trough CsA levels were measured by an enzyme multiplied immunoassay technique (EMIT 2000 TDM; Siemens Healthcare Diagnostics) immediately before the morning dose. Comparisons used one-way analysis of variance (ANOVA) across multiple time points and the Student *t* test for paired data between specific target time points, with statistical significance accepted for $P < 0.05$. Statistical analysis was performed using SPSS software packages (version 17; IBM).

Our results confirm that posaconazole increases blood CsA levels in allo-BMT recipients ($P = 0.011$; Table 2) and also show that a significant effect can already be detected within the first week of combined treatment ($P = 0.028$). In keeping with this effect on blood CsA levels and on the basis of clinical criteria, the daily dose of CsA was adjusted during combined treatment from 3.09 ± 1.01 mg/kg at the baseline down to 1.58 ± 0.82 mg/kg on day 30 ($P = 0.028$), which represents an approximately 50% dose reduction. However, this CsA dose reduction was not clinically required upfront during the first week (3.06 ± 1.1 on day 7; $P = 0.857$) because it occurred normally by day 14 ($P = 0.082$) and most frequently in the last 2 weeks of combined treatment ($P < 0.001$). The clinical magnitude of this drug-drug interaction is best described by the CsA concentration-to-dose ratio (2), which shows a significant steady increase with time ($P < 0.001$). The blood posaconazole levels in this study are not available, and an association between blood posaconazole and CsA levels could not be analyzed. Our strategy was safe and well tolerated from a clinical perspective (Table 3). Only seven patients (17%) had CsA-related toxicities, including renal dysfunction ($n = 4$), hypertension ($n = 1$), essential tremor ($n = 1$), and mild thrombotic microangiopathy ($n = 1$), all of which resolved with dose adjustment, as planned.

Interactions among azoles and immunosuppressive drugs are important in the clinical management of transplant recipients. Since the approval of posaconazole in allo-BMT, increasing evidence has emerged on the effect of CsA and other drugs and factors on posaconazole pharmacokinetics (8, 20), as well as on the effect of posaconazole on the management of immunosuppressive drugs such as tacrolimus (2) and sirolimus (9, 13). However, very little is known about the impact of posaconazole on CsA. The original prescribing information recommendation to reduce the dose of CsA upon the initiation of combined treatment with posaconazole (17) results from a study of only four cardiac transplant recipients, three of whom required a CsA dose reduction because of important decreases in its clearance (16). The only report on the impact of posaconazole on CsA in allo-BMT comes in abstract format in a subset of 19 patients from the registration trial whose blood CsA level data were available, showing an increase in the CsA concentration-to-dose ratio after the start of posaconazole (10). Unfortunately, levels were assessed only twice, at the baseline and 2 weeks from the start of combined treatment, and neither earlier time points nor the need for upfront dose adjustment was analyzed. From 1988, when Yee et al. first reported a significant association between low trough CsA concentrations and the risk of developing acute GVHD the following week (19), it is well established that subtherapeutic CsA levels after allo-BMT have a negative impact on transplant outcome (5, 6, 11, 12, 14). In order to avoid such subtherapeutic CsA levels, even transiently, general practice developed to widely accept that in the absence of toxicity, high blood CsA levels up to twice the upper limit of the therapeutic range would not require a dose reduction (1). While CsA dose reduction might have less of an impact in patients with GVHD, who are concomitantly receiving high-dose steroids and other immunosuppressive drugs, in the early phase of allo-BMT, the achievement and maintenance of therapeutic blood CsA levels is critical to prevent GVHD.

To the best of our knowledge, this is the first study that analyzed the impact of posaconazole on the management of CsA in the early phase of allo-BMT. Our results confirm that posacona-

TABLE 3 Laboratory safety data on combined CsA and posaconazole treatment of allogeneic BMT recipients[a]

Time point	Bilirubin	ALT	AST	Creatinine
Day 0	1 (2.4); 16.7 ± 12.9, 12 (3–62)	2 (4.8); 0.85 ± 0.89, 0.48 (0.14–3.74)	1 (2.4); 0.64 ± 0.72, 0.43 (0.13–4.63)	0; 72 ± 20.5, 68 (42–124)
Day 7	0; 19.7 ± 10.8, 17 (3–41)	2 (4.8); 0.75 ± 0.79, 0.45 (0.11–3.77)	0; 0.45 ± 0.44, 0.34 (0.02–2.92)	0; 76 ± 30.7, 68 (41–202)
Day 14	3 (7.3); 22.4 ± 16.9, 17 (3–77)	1 (2.4); 0.85 ± 1.63, 0.47 (0.03–10.42)	0; 0.56 ± 0.53, 0.4 (0.04–2.85)	0; 82.5 ± 36.4, 79 (40–188)
Day 30	1 (2.4); 19.9 ± 12.0, 17 (5–56)	1 (2.4); 0.78 ± 0.81, 0.47 (0.09–4.69)	0; 0.56 ± 0.38, 0.43 (0.06–2.17)	0; 89.4 ± 27.5, 86 (44–180)

[a] Data are expressed both as the number (percentage) of cases with grade III to IV toxicity (CTCAE v3.0) and as the mean bilirubin (μmol/liter), alanine transaminase (ALT; μkat/liter), aspartate transaminase (AST; μkat/liter), or creatinine (μmol/liter) level ± the standard deviation and median (range) in all cases.

zole treatment leads to an increase in blood CsA levels and an overall 50% reduction in the dose of CsA over the course of a few weeks. While the potential risk derived from subtherapeutic CsA levels following an upfront reduction of the CsA dose may depend on the type of allo-BMT, the timing of the reduction, or the concomitant use of other immunosuppressive drugs, our data clearly show that an upfront CsA dose reduction is not required to manage these patients despite the significant increase in levels from the first week of combined treatment. In addition, since it is difficult to isolate and predict the independent effect on CsA levels of posaconazole from that of other drugs and factors in such complex patients, it would also appear more cautious not to automatically reduce the CsA dose in all cases upfront but rather let changes be guided by therapeutic drug monitoring. Our recommendation is to maintain CsA at the initiation of combined treatment with posaconazole and to subsequently adjust the CsA dose on the basis of individualized patient results of close monitoring of blood CsA levels a minimum of three times weekly and clinical toxicity. In our study, this strategy has been shown to be safe and effective in the early phase of allo-BMT.

ACKNOWLEDGMENT

This work was partly funded by an unrestricted research grant from Schering-Plough Corporation (presently Merck & Co., Whitehouse Station, New Jersey).

REFERENCES

1. **Applebaum FR, Forman SJ, Negrin RS, Blume KG.** 2009. Pharmacologic prevention of acute graft-versus-host disease, p 1257–1274. *In* Applebaum FR, Forman SJ, Negrin RS, Blume KG (ed), Thomas' hematopoietic cell transplantation, 4th ed. Blackwell Publishing, Ltd., Oxford, United Kingdom.
2. **Berge M, et al.** 2009. Safe management of tacrolimus together with posaconazole in lung transplant patients with cystic fibrosis. Ther. Drug Monit. **31**:396–399.
3. Reference deleted.
4. **Farowski F, Vehreschild JJ, Cornely OA.** 2007. Posaconazole: a next-generation triazole antifungal. Future Microbiol. **2**:231–243.
5. **Ghalie R, Fitzsimmons WE, Weinstein A, Manson S, Kaizer H.** 1994. Cyclosporine monitoring improves graft-versus-host disease prophylaxis after bone marrow transplantation. Ann. Pharmacother. **28**:379–383.
6. **Kanda Y, et al.** 2006. Effect of blood cyclosporine concentration on the outcome of hematopoietic stem cell transplantation from an HLA-matched sibling donor. Am. J. Hematol. **81**:838–844.
7. **Keating GM.** 2005. Posaconazole. Drugs **65**:1553–1567.
8. **Kohl V, et al.** 2010. Factors influencing pharmacokinetics of prophylactic posaconazole in patients undergoing allogeneic stem cell transplantation. Antimicrob. Agents Chemother. **54**:207–212.
9. **Kubiak DW, et al.** 2012. Safety of posaconazole and sirolimus coadministration in allogeneic hematopoietic stem cell transplants. Biol. Blood Marrow Transplant. **18**:1462–1465.
10. **Langston A, Lipton JH, Brundage T, Patinmo H, Ullmann AJ.** 2007. Impact of posaconazole vs fluconazole on cyclosporine and tacrolimus dosing in hematopoietic stem cell transplant recipients with graft-versus-host disease. Biol. Blood Marrow Transplant. **13**(Suppl. 2):76.
11. **Malard F, et al.** 2010. Impact of cyclosporine-A concentration on the incidence of severe acute graft-versus-host disease after allogeneic stem cell transplantation. Biol. Blood Marrow Transplant. **16**:28–34.
12. **Martin P, et al.** 2003. Relationship between CsA trough blood concentration and severity of acute graft-versus-host disease after paediatric stem cell transplantation from matched-sibling or unrelated donors. Bone Marrow Transplant. **32**:777–784.
13. **Moton A, et al.** 2009. Effects of oral posaconazole on the pharmacokinetics of sirolimus. Curr. Med. Res. Opin. **25**:701–707.
14. **Przepiorka D, et al.** 1991. Cyclosporine and methylprednisolone after allogeneic marrow transplantation: association between low cyclosporine concentration and risk of acute graft-versus-host disease. Bone Marrow Transplant. **7**:461–465.
15. **Sánchez-Ortega I, et al.** 2011. Clinical efficacy and safety of primary antifungal prophylaxis with posaconazole vs itraconazole in allogeneic blood and marrow transplantation. Bone Marrow Transplant. **46**:733–739.
16. **Sansone-Parsons A, et al.** 2007. Effect of oral posaconazole on the pharmacokinetics of cyclosporine and tacrolimus. Pharmacotherapy **27**:825–834.
17. **Schering Corporation.** 2008. Prescribing information for Noxafil (posaconazole) oral suspension. Schering Corporation, Kenilworth, NJ.
18. **Ullmann AJ, et al.** 2007. Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N. Engl. J. Med. **356**:335–347.
19. **Yee GC, et al.** 1988. Serum cyclosporine concentration and risk of acute graft-versus-host disease after allogeneic marrow transplantation. N. Engl. J. Med. **319**:65–70.
20. **Zhuang D, et al.** 2008. Effect of calcineurin inhibitors on posaconazole blood levels as measured by the MVista microbiological assay. Antimicrob. Agents Chemother. **52**:730–731.